



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/127,364	07/31/1998	THEODORE A. YEDNOCK	193-US-CIP2	1040

7590 07/02/2004

GERALD F. SWISS ESQ.  
FOLEY & LARDNER  
THREE PALO ALTO SQUARE  
3000 EL CAMINO REAL, SUITE 100  
PALO ALTO, CA 94306-2121

EXAMINER

LUKTON, DAVID

ART UNIT	PAPER NUMBER
----------	--------------

1653

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/127,364

**Applicant(s)**

YEDNOCK ET AL.

**Examiner**

David Lukton

**Art Unit**

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 30 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 48-59 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 48-59 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: \_\_\_\_\_.

Pursuant to the directives of the amendment filed 4/30/04, the previously pending claims (claims 1-47) have been cancelled, and claims 48-59 added. Claims 48-59 are now pending.

Applicants' arguments filed 4/30/04 have been considered and found persuasive in part. The rejection of claim 39 under 35 U.S.C. §112, first paragraph (new matter) is withdrawn. In addition, the previously imposed prior art rejections are withdrawn (assuming that each of claims 56, 58 and 59 is intended to be dependent on one of the currently pending claims).



Claims 48-50 and 54 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 58-59 of copending application Serial No. 09/987619, or claims 33-34 of 10/316205. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 48 does not require that the treatment (if and when successful) is effective solely because of VLA-9 antagonism. In fact, the claims do not require that the efficacy of the compound is due in part to antagonism of VLA-9. The claims encompass the possibility that the efficacy is due entirely to a mechanism that is independent of VLA-9 antagonism. Moreover, some of the diseases to be treated are the same in the instant application, and the two copending applications. [This is a *provisional* obviousness-type double patenting

rejection because the conflicting claims have not in fact been patented]

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).



The following is a quotation of the first paragraph of 35 U.S.C. §112:

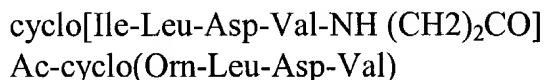
The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 48-59 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated on page 32, line 3+, each of the compounds of examples 1-373 of application 08/904424 exhibited an  $IC_{50}$  of 15 micromolar or less in an assay which measures antagonism of the compounds to VLA-4. It does not appear that applicants have tested the compounds in an assay of  $\alpha$ -9 integrin antagonism; if applicants are asserting that there exists a correlation between the propensity of a compound to antagonize VLA-4, and the propensity of the compound to antagonize *alpha*-9 integrin,

such an assertion will be left unchallenged at the present time. However, to the extent that such overlap exists, a finding of unpredictability in VLA-4 antagonism will extend to  $\alpha_4\beta_1$  antagonism as well. The assertion by the examiner is that (a) structure/activity relationships in VLA-4 antagonism are unpredictable, and (b) treatment of inflammatory conditions is unpredictable as well. Consider the following:

- Dutta (*Journal of Peptide Science* **6**, 321-341, 2000) has examined the efficacy of various peptides in the antagonism of VLA-4/VCAM-1 binding. As stated on page 329, col 2, last two lines, the following two compounds were inactive both *in vitro* and *in vivo*:



These peptides are minor variations of peptides that were active.

- Arrhenius (*USP 5,688,913*) discloses (cols 17-18) several examples of compounds which failed to antagonize VLA-4. These compounds are minor variations of other compounds that were potent antagonists of VLA-4.
- Komoriya, Akira (*J. Biol. Chem.* **266** (23), 15075-15079, 1991) discloses that in an assay of  $\alpha_4\beta_1$  activity, the pentapeptide EILEV was active, but pentapeptide EILDV was not. This latter peptide differs from the former by just one methylene unit.
- Haworth, Duncan (*Br. J. Pharmacol.* **126**(8), 1751-1760, 1999) discloses various VLA-4 antagonists. At least one of the disclosed compounds was inactive; this compound differed by only a few methylene units from a compound that was active.
- Haubner (*J. Am. Chem. Soc.* **118**, 7881, 1996) discloses (table 2) two compounds which failed to inhibit fibrinogen binding to the  $\alpha_{IIb}\beta_1$  receptor, and vitronectin binding to the  $\alpha_v\beta_3$  receptor. The reference also discloses (p. 7882, col 2) that replacement of glycine with alanine in RGD results in a "drastic loss" of activity. These data argue for "unpredictability" in structure activity relationships of integrins generally. In addition, the "unpredictability" in structure activity relationships of RGD-peptides has direct relevance to the claimed compounds. As disclosed in Yang Y (*European Journal of Immunology* **28** (3) 995-1004, 1998) RGD-containing

peptides can bind to VLA-4. Thus, if one cannot predict structure activity relationships of RGD peptides in their binding to VLA-4, it stands to reason that such unpredictability extends to other compounds which either do bind VLA-4, or which are asserted to exhibit such an effect.

In addition to the foregoing, the following references teach "failure" in the treatment of one or more inflammatory conditions:

Vatistas N J, "Infection of the intertubercular bursa in horses: four cases (1978-1991)", [*Journal of the American Veterinary Medical Association* **208** (9) 1434-7, 1996];

Tait A, "Synthesis and antiinflammatory activity of 2,6-bis(1,1- dimethylethyl) phenol derivatives" (*Farmaco* **48** (10) 1463-73, 1993);

Kurokawa M "Synthesis and antiinflammatory activity of cis- and trans- 6,6a, 7,8,9,10,10a,11- octahydro-11-oxodibenzo[b,e]thiepinacetic and -oxepinacetic acids" (*Journal of Medicinal Chemistry* **33** (2) 504-9, 1990);

Uren M F, "The effect of anti-inflammatory agents on the clinical expression of bovine ephemeral fever" (*Veterinary Microbiology* **19** (2) 99-111, 1989);

Crossley M J, "Studies on the effects of pharmacological agents on antigen-induced arthritis in BALB/c mice" (*Drugs Under Experimental and Clinical Research* **13** (5) 273-7, 1987).

Thus, structure/activity relationships involving VLA-4 are unpredictable. Perhaps it is true that many of the compounds falling within the scope of claim 35 will exhibit an IC<sub>50</sub> of 15 micromolar in an assay of VLA-4. However, the significance of this number (15 µM) with respect to treatment of treatment of Alzheimer's disease, AIDS dementia, diabetes, atherosclerosis, multiple sclerosis, inflammatory bowel disease, stroke, nephritis, asthma,

retinitis, atopic dermatitis, psoriasis, and myocardial ischemia is unknown. No correlation has been established between this "15  $\mu$ M" parameter, and successful treatment of any of the foregoing diseases. Moreover, other issues such as bioavailability and pharmacokinetics are not reflected in this "15  $\mu$ M" number.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As is evident, extrapolation from an observation of VLA-4 binding in vitro to treatment of Alzheimer's disease, AIDS dementia, diabetes, atherosclerosis, multiple sclerosis, inflammatory bowel disease, stroke, nephritis, asthma, retinitis, atopic dermatitis, psoriasis, and myocardial ischemia will produce "unpredictable" results.

Clearly then, "undue experimentation" would be required to practice the claimed invention.

In addition to the foregoing arguments, consider the following:

- Pierce, J. W., ("Salicylates inhibit I kappa B-alpha phosphorylation, endothelial-leukocyte adhesion molecule expression, and neutrophil transmigration", *Journal of Immunology*, 156 (10) 3961-9, 1996) discloses that aspirin inhibits ICAM-1 and VCAM-1 expression. In a similar vein, Gonzalez-Alvaro I ("Interference of nonsteroidal antiinflammatory drugs with very late activation antigen 4/vascular cells adhesion molecule 1-mediated lymphocyte-endothelial cell adhesion", *Arthritis and Rheumatism* 41 (9) 1677-88,

1998) discloses that indomethacin inhibits VLA-4/VCAM-1 interactions. If applicants' assertions were correct, the skilled artisan would predict that success in the treatment of inflammatory conditions would be achieved by any compound which antagonizes VLA-4/VCAM-1 interactions. Yet this is not what one finds. For example, Goldenberg M M ("A pharmacologic analysis of the action of platelet-activating factor in the induction of hindpaw edema in the rat", *Prostaglandins* 28 (2) 271-8, 1984) discloses that neither indomethacin nor aspirin was effective to inhibit an inflammatory response to paw edema in rats. Similarly, Zuany-Amorim C. (*European Journal of Pharmacology* 257 (3) 211-6, 1994), discloses that aspirin failed to inhibit inflammatory responses to antigen (e.g., page 214, col 1). These findings of Goldenberg and of Zuany-Amorim support the examiner's contention that one cannot predict success in the treatment of inflammatory diseases merely because one can antagonize VLA-4/VCAM-1 interactions in vitro. As two more examples, Rordorf C "Arthritis in MRL/LPR mice and in collagen II sensitized DBA-1 mice and their use in pharmacology", *International Journal of Tissue Reactions* 9 (4) 341-7, 1987 discloses that indomethacin was not effective to treat arthritis in an animal model, and Goldlust M B (*Agents and Actions* 11 (6-7) 729-35, 1981) discloses that aspirin was not effective to treat synovitis in rabbits.

- Theien, B. E. (*Journal of Clinical Investigation* 107 (8) 995-1006, 2001) compared the ability of anti-VLA-4 to regulate proteolipid protein (PLP) 139-151-induced R-EAE when administered either before or after disease onset. Preclinical administration of anti-VLA-4 either to naive recipients of primed encephalitogenic T cells or to mice 1 week after peptide priming, i.e., before clinical disease onset, inhibited the onset and severity of clinical disease. In contrast, Ab treatment either at the peak of acute disease or during remission exacerbated disease relapses and increased the accumulation of CD4(+) T cells in the CNS. Most significantly, anti-VLA-4 treatment either before or during ongoing R-EAE enhanced Th1 responses to both the priming peptide and endogenous myelin epitopes released secondary to acute tissue damage. Collectively, these results suggest that treatment with anti-VLA-4 Ab may be problematic in treating established autoimmune diseases such as MS. Accordingly, one cannot predict success in the treatment of MS based on the propensity of a compound to antagonize VLA-4.
- Saez-Torres I ("Peptide T does not ameliorate experimental autoimmune encephalomyelitis (EAE) in Lewis rats", *Clinical and Experimental Immunology*



121 (1) 151-6, 2000) discloses that it is known in the art that peptide T inhibits T cell activation and cytokine production and function. Saez-Torres studied the ability of peptide T to ameliorate EAE in Lewis rats. Peptide T was administered subcutaneously at different doses and phases of the disease according to several treatment protocols. The authors concluded that peptide T neither prevents nor ameliorates EAE in Lewis rats. This supports the conclusion that one cannot "predict" success in the treatment of inflammatory conditions, even if one is able to inhibit T cell activation and cytokine production. This finding of Saez-Torres is relevant in part because VLA-4 is prominently expressed on circulating T-cells.

The foregoing teachings further support the conclusion that one cannot predict efficacy in the treatment of human disease merely by modulating *alpha* 4/ligand interactions *in vitro* (or VLA-9/ligand interactions). Clearly, "undue experimentation" would be required to practice the claimed invention.

In response to the foregoing, applicants have begun with the following:

"The instant specification imputes alpha-9 integrin antagonism based, inter alia, on empirically-determined data with respect to VLA-4 antagonism. Therefore, the level of unpredictability that may exist in the area of VLA-4 antagonist structure-function is not relevant since the relevant VLA-4 antagonists have been identified experimentally, thereby traversing any perceived scientific hurdle with respect to VLA-4 antagonist structure-function predictions".

Applicants have also pointed to various locations in the specification where they argue support may be found. However, most of the cited passages do not even mention VLA-9 or alpha-9. The specification only argues that antagonists of VLA-4 will be "candidates" for binding to VLA-9. However, an assertion that a compound is a "candidate" for something is by no means equivalent to a showing of an activity. Despite all of applicants arguments, it remains the case that there is no evidence that any of the claimed

compounds are effective to antagonize alpha-9. Nor have applicants even argued that as of July, 1997, the skilled artisan would have believed that if a compound is effective to antagonize alpha-4, it will also be effective to antagonize alpha-9. In accordance with the foregoing, claim 55 would lack enablement, even if it did not recite the term "pharmaceutically effective".

Next (page 10) of the response, applicants have made arguments regarding utility. However, the examiner has not argued that utility for the claimed invention is lacking. Accordingly, there is no need for applicants to argue that a rejection for lack of utility would be improper, had it been imposed.

Next, applicants have argued the following:

"...the Patent Office appeared to place significant weight on published reports of 'failure' in the treatment of inflammatory conditions to support the proposition that treatment of the diseases recited in the claims was not enabled by the specification. Applicants recognize that "failure" is part of the scientific process. Applicants need not articulate what those skilled in the art know so well. Yet, by its statements, the Patent Office appears to be asserting that prior reported failures in a particular area of research may be used as objective evidence to challenge Applicants' disclosure. Office Action at page 8. No doubt, a large number of compositions, or method of use thereof, have failed to treat certain human diseases, disorders, and/or conditions. However, precluding patentability of novel compounds in view of the failure of others would lead to absurd results in virtually all areas of patent practice".

The examiner's first point is that "failure" *per se* in the treatment of inflammatory diseases is not the basis for the rejection. Rather, the question is that of predictability of success in the treatment of inflammatory diseases based solely on the acquisition of an

*in vitro* result. Applicants have not even obtained such an *in vitro* result in the case of alpha-9, but should applicants choose to provide such at some point in the future, the question of extrapolation from the “test tube” to the intact animal will then come into play. As indicated above, applicants have argued the following:

“...precluding patentability of novel compounds in view of the failure of others would lead to absurd results in virtually all areas of patent practice”.

The first point is that “all areas of patent practice” are not relevant. For example, what may constitute an appropriate analysis of enablement in the field of organic chemistry would not necessarily have any meaning in the field of mechanical engineering. And what may constitute an appropriate analysis of enablement in the field of organic chemistry is not necessarily going to be applicable where therapeutic method claims are concerned. More to the point, the standards for enablement of a claim drawn to a compound *per se* are different from the standards of a claim drawn to a method of treating a disease. The examiner has made no argument, and has not even attempted to imply that if the claims had been drawn to compounds *per se*, and if the genus of compounds thus claimed were the same as the genus of compounds recited in claim 48, that an enablement rejection would be appropriate. Thus, attempting to commingle enablement issues that might be applicable to compounds *per se* with enablement issues that apply to therapeutic method claims constitutes an unproductive venture.

Next applicants have argued that data is presented which shows that the compounds to

which the claims are drawn are effective to antagonize VLA-4. This particular point has not been challenged by the examiner. Next, applicants argue (page 11, response) that “binding to VLA-4 is predictive of binding to alpha-9 integrin”, and argue that evidence of this can be found on pages 18-19 of the specification. However, the specification only asserts that VLA-4 antagonists are “candidates” for testing in an assay that measures alpha-9 antagonist propensity.

Next, applicants have made the following argument:

The language of the rejection also appeared to require that Applicants provide experimental evidence of the treatment of certain diseases and address issues related to bioavailability and pharmacokinetics. By making such a requirement, the Patent Office would essentially preclude patenting of a compound until it had been evaluated in advanced clinical studies. This has never been the law for patenting small molecule pharmaceutical compounds. By requiring a patent applicant to provide such data, in exchange for patent protection, the Patent Office would force inventors to delay applying for patent protection until late in the drug discovery process, once significant financial capital has been invested in a drug. From a policy standpoint, Applicants submit that drug discovery would be adversely affected if patent protection was only available after such an enormous expenditure. Moreover, Applicants are well aware that it is not typical for the Patent Office to require pharmacokinetic and bioavailability data for the patenting of novel pharmaceutical compounds. Accordingly, the basis for the instant enablement rejection is inconsistent with both PTO policy and practice.

In response, the examiner has never argued that human clinical data is required.

Accordingly, attributing such a statement to the examiner does not help advance the process.

With regard to applicants assertion that [the examiner’s rejection] would force inventors to delay applying for patent protection until late in the drug discovery process, it appears that

applicants are again attempting to commingle issues which are pertinent to claims that are drawn to compounds with issues that are drawn to therapeutic methods. However, commingling such issues is not productive. To reiterate the point made above, examiner has made no argument, and has not even attempted to imply that if the claims had been drawn to compounds *per se*, and if the genus of compounds thus claimed were the same as the genus of compounds recited in claim 48, that an enablement rejection would be appropriate. Further, there is an argument to be made that a claim drawn to a method of inhibiting binding between VLA-4 and a VLA-4 ligand would be enabled. However, no such claim is pending at the present time. The point is that there is much that can be patented based solely on *in vitro* data. It is true, however, that when an enablement rejection is imposed against a therapeutic method claim, greater effort is likely to be required by an inventor than would be required of claims drawn to compounds *per se*. As for the issue of bioavailability and pharmacokinetics, the examiner has not argued that this is a requirement *per se*. But in the event that applicants can show that the compounds (to which the claims are drawn) are effective inhibitors of alpha-9, the central issue will be whether the skilled artisan can "predict" therapeutic efficacy based on this *in vitro* finding.

In endeavoring to ascertain whether such a prediction can be reliably made, it is appropriate to consider all pharmacological factors. Among the factors which are relevant are bioavailability and pharmacokinetics. In the event that applicants can show that the subject compounds are indeed effective to treat various inflammatory diseases (such

as atherosclerosis, vascular occlusion, arthritis, Crohn's Disease), it would be appropriate at that point to revisit the matter of bioavailability and pharmacokinetics. But as long as the issue is that of "unpredictability" (in the extrapolation from the "test tube" to the diseased animal), it is appropriate to consider a range of pharmacological and physiological factors.

Next, applicants have argued that they have provided "drug screening assays", and an "animal model". However, these are only invitations to others to experiment. Such an invitation does not show the skilled artisan how to use the compounds (to which the claims are drawn) to treat inflammatory disease in mammals.

Next, applicants have argued (page 12, response) essentially that to discover which compounds will be effective to treat inflammatory disease and under what conditions would require only "routine" experimentation if undertaken by others, yet would require (it is implied) "undue" experimentation if undertaken by applicants. However, this is found unpersuasive, and appears on its face to be contradictory.

It is maintained that "undue experimentation" would be required to determine which, if any, of the compounds (to which the claims are drawn) will be effective to antagonize alpha-9 *in vitro*; and that "undue experimentation" would be required to determine which, if any, of the compounds will be effective to treat inflammatory diseases, and under what conditions.

It is suggested that applicants do the following: (a) cancel claim 48, and all claims dependent thereon, (b) provide data showing that the compounds to which the claims are drawn are effective to antagonize alpha-9 *in vitro*, and (c) delete the phrase

“pharmaceutically effective dosage” from claim 55.



Claims 48-59 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Each of claims 56, 58 and 59 is dependent on a cancelled claim.
- Claims 48-53 are indefinite as to the intended inflammatory conditions.
- Claim 55 recites the phrase “pharmaceutically effective”, thus rendering the claims indefinite as to the objectives of the pharmaceutically efficacy. Suppose that the compound is injected into each of two rats. The “first” rat is injected with an amount of the compound which is effective to inhibit binding of an alpha 9 integrin to an alpha-9 integrin ligand, but which amount is not, at the same time, “pharmaceutically effective”. The “second” rat is injected with an amount of the compound which is not only effective to inhibit binding of an alpha integrin to an alpha-9 integrin ligand, but is also “pharmaceutically effective”. What difference, exactly, would the practitioner perceive between the two rats subsequent to injection?
- In claim 59, the phrase “*alpha-4/beta-1*” lacks antecedent basis.



No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

  
**DAVID LUKTON  
PATENT EXAMINER  
GROUP 100**